EXHIBIT 12

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE: Acetaminophen – ASD–ADHD Products Liability Litigation **This Document Relates To: All Actions**	**22-md-3043 (DLC)**

REBUTTAL EXPERT REPORT OF
DR. ERIC HOLLANDER, M.D., DFAPA, FACNP

I. EXECUTIVE SUMMARY

The following report is provided pursuant to Rule 26 of the Federal Rules of Civil Procedure. I have been asked to address certain opinions presented in the Defendants' expert reports. Some of the opinions expressed in the reports of Dr. Faraone and Dr. Kolevzon are contrary to the opinions and analysis presented in my initial report dated June 16, 2023 (amended June 23, 2023) ("Initial Report"). I stand by the opinions and analysis in my Initial Report, and therefore do not intend to present further rebuttal on every point in the Defendants' experts' reports with which I respectfully disagree. In addition, the expert reports of Dr. Baccarelli, Dr. Cabrera, Dr. Pearson, and Dr. Louie contain opinions and analysis that refute or qualify some of the opinions in the Defendants' experts' reports. Finally, I understand that the other experts are preparing rebuttal reports that further refute or qualify certain opinions in the reports of Defendants' experts. All of my opinions here are offered to a reasonable degree of scientific certainty.

The materials that I have relied upon in forming my opinions include those I considered in preparing my Initial Report and additional materials identified in the list of materials submitted with this report. I have based my opinions on my background, education, experience, and

knowledge, my own review of the medical and scientific literature, as well as the materials provided to me.

Dr. Faraone states: “There is no reliable scientific evidence that maternal use of acetaminophen causes ADHD in offspring,” and the Bradford Hill “criteria do not support a causal inference.” (Faraone Report at 3-4). Dr. Kolevzon states: “the observational epidemiological studies evaluating whether maternal use of acetaminophen during pregnancy is associated with ASD in offspring . . . do not furnish reliable scientific evidence of an association between maternal acetaminophen use during pregnancy and the development of ASD in offspring,” and therefore “a causality analysis using traditional methods, such as the Bradford Hill criteria, is not warranted.” (Kolevzon Report at 43). I respectfully disagree with Dr. Faraone and Dr. Kolevzon. The Bradford Hill analysis contain in this report illustrates the shortcomings of the analyses and opinions of Dr. Faraone and Dr. Kolevzon.

In my opinion, to a reasonable degree of scientific and medical certainty (and more likely than not), prenatal exposure to acetaminophen (APAP or paracetamol) at therapeutic doses can cause the neurodevelopmental disorders of Autism Spectrum Disorders (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD). My analysis at this phase is limited to questions of general causation.

As described in greater detail in my Initial Report, I am a licensed psychiatrist with expertise in psychopharmacology and neuropsychopharmacology, and I rely on that expertise to review and analyze the scientific evidence relating to the association between in utero APAP exposure and the neurodevelopmental disorders, ASD, and ADHD. I routinely assess potential causal associations between a substance and a pharmacological effect as part of my research work.

I have also undertaken these assessments as part of my clinical practice specializing in neuropsychopharmacology and neurodevelopmental disorders.

In evaluating the evidence of an association between prenatal APAP exposure and ASD and ADHD in offspring in this report, I draw on my experience as a medical doctor who has treated and researched ASD and ADHD using a comprehensive, transdiagnostic approach. There is strong epidemiological evidence that the association between prenatal APAP exposure and ASD and/or ADHD diagnoses is causal. As demonstrated in Dr. Baccarelli's report, researchers have undertaken numerous well-designed scientific studies across large and different populations and found significant positive associations between mothers who ingested APAP during pregnancy and subsequent neurodevelopmental disorders with ASD and/or ADHD symptoms in the offspring. These studies accounted for measurable confounders, such as maternal age, smoking, drinking, and genetics, yet the results of a positive association between APAP use and ASD and ADHD hold true. Based on my review of this scientific evidence, along with my education, training, decades of clinical and research experience, and a review of information from regulators and manufacturers, I conclude that this association is indeed causal.

To reach that conclusion, I applied a weight of the evidence methodology with the same scientific rigor that I use in my research and clinical practice. Briefly, I utilized a weight of the evidence approach guided by the Bradford Hill factors. In conducting a Bradford Hill analysis, I assigned the most weight to the factors of (1) dose response, (2) biological plausibility, (3) coherence, (4) consistency, and (5) strength of association; moderate weight to the factor of specificity; and little weight to the factors or experimental evidence and analogy. As described in greater detail below, I determined the weight of the evidence satisfies all of the Bradford Hill factors except for specificity. Importantly, specificity is "widely considered weak or irrelevant"

(Fedak, 2015) because many causal associations do not satisfy this element. And it is not surprising that specificity is not satisfied here given the highly heterogenous etiology of neurodevelopmental disorders like ASD and ADHD.

The evidence amply satisfies the criteria to which I accord the greatest weight. In particular, there is an observed dose response in the studies that evaluated dose response, which, while not a prerequisite for a causal finding, is highly probative as to causation. There are plausible biological mechanisms as discussed in my Initial Report, published literature, and Dr. Cabrera's report. The scientific literature—including the vast majority of 29 observational studies involving over 220,000 mother-child pairs from around the world—shows a consistent and statistically significant positive association between prenatal APAP exposure and neurodevelopmental disorders. The association identified is also coherent with existing knowledge about neurodevelopment disorders and the vulnerability of the prenatal brain. Taken as a whole, based on my extensive training and experience, I conclude the scientific evidence shows that in utero APAP exposure can cause the neurodevelopmental disorders of ASD and ADHD.

I express the opinions set forth herein to a reasonable degree of medical and scientific certainty. In reaching these conclusions, I have followed the same or similar methodology and procedures that I employ in my clinical practice and in the clinical study of neurodevelopmental disorders, including ASD and ADHD. I have not used special or different procedures in preparing this report.

II. QUALIFICATIONS AND EXPERIENCE

My qualifications and experience are set forth in my Initial Report.

III. METHODOLOGY

In my clinical and research practice, I frequently make assessments of potential causal associations between a substance and a particular pharmacological adverse effect. Ultimately, I make determinations as to whether exposure to a particular drug or medicine causes or increases the risk of a particular neurodevelopmental or psychiatric outcome or effect. When determining whether a causal relationship exists, I utilize a weight of the evidence approach.

A. Overview of the Bradford Hill Methodology

Just as in my clinical and research practice, the weight of the evidence analysis that I employ here considers the Bradford-Hill factors as part of a framework to analyze the cumulative weight of the evidence (Bradford Hill, 1965). The Bradford-Hill factors are a set of factors used to assess the evidence of causality between an exposure and a disease. These elements were proposed by the British epidemiologist Sir Austin Bradford Hill in 1965. The nine Bradford-Hill factors are:

a. <u>Strength of Association:</u> A stronger association between the exposure and the disease increases the likelihood of a causal relationship.

b. <u>Consistency:</u> The association is observed consistently in different studies, populations, and settings.

c. <u>Specificity:</u> The exposure is specifically associated with the outcome and not with a wide range of other outcomes.

d. <u>Temporality:</u> The exposure precedes the development of the disease in a temporal sequence.

e. <u>Biological Gradient (Dose-Response Relationship):</u> There is a dose-response relationship, meaning that higher levels or longer duration of exposure are associated with a higher risk of the disease.

f. Plausibility: The proposed mechanism of causation is biologically plausible and supported by existing knowledge.

g. Coherence: The association is coherent with existing knowledge and does not conflict with established biological or medical principles.

h. Experiment: Experimental evidence, such as randomized controlled trials, supports the causal relationship.

i. Analogy: Similarities between the relationship being studied and other established causal relationships can provide supporting evidence.

These elements are not intended to be a definitive checklist, but rather a set of considerations that can be used together to evaluate the strength of evidence for causality. In assessing the causal association between prenatal exposure to APAP during pregnancy and development of neurodevelopmental disorders, including ASD and ADHD, in offspring, I applied the Bradford-Hill elements described above, though no element alone is determinative of causation.

B. Weight Given to Each Bradford-Hill Element

I do not assign each of the Bradford-Hill elements equal weight because some factors are more important than others in determining whether a causal relationship can be inferred. For example, as described below, temporality is a necessary criterion, but it alone is not sufficient to show causation. It should, therefore, be accorded more weight than a criterion like specificity, which is often not present in true causal relationships. When I perform Bradford Hill analyses, I generally assign weight to each element as follows:

a. Biological Gradient: To the extent an exposure is capable of being measured, the identification of a biological gradient, or dose-response curve, is an important

component of a causation analysis to which I place significant weight. Although dose response is not a necessary factor to make a causation determination, it is highly probative of a causal association.

b. Plausibility: While identification of biologically plausible mechanisms of action lends support to the causal relationship between the exposure and disease, lack of certainty in this regard is expected and does not weigh against causation. In fact, Bradford Hill cautions that "this is a feature I am convinced we cannot demand. What is biologically plausible depends on the biological knowledge of the day. . . . In short, the association we observe may be one new to science or medicine and we must not dismiss it too light-heartedly as just too odd. As Sherlock Homes advised Dr. Watson, 'when you have eliminated the impossible, whatever remains, *however improbable*, must be the truth'" (Bradford Hill, 1965 (emphasis in original)). Thus, I assign significant weight to the identification of biologically *plausible* mechanisms of action, with an emphasis on plausibility rather than certainty.

c. Consistency: An association that has been "repeatedly observed by different persons, in different places, circumstances and times" is convincing evidence of causality (Bradford Hill, 1965). Consistency of an association across multiple studies of different types, employing different methods, examining different populations reduces the chance that an association is due to a flaw in the study design. I ascribe significant weight to this element.

d. Coherence: According to Bradford Hill, an association must not "fundamentally contradict present substantive knowledge" of the exposure and disease (Bradford Hill, 1965). Rather, the causal association must cohere to the present understanding

of how an exposure relates to the disease. This element has been described as "being similar to biological plausibility, in that the cause-and-effect story should make sense with all available knowledge to the researcher" (Fedak et al., 2015). I agree with this position and, therefore, ascribe significant weight to this element.

e. Strength of Association: Bradford Hill lists strength of association first in his list of elements. While a stronger association—in terms of greater odds ratio—is powerful evidence in support of causation, Bradford Hill warns, "[w]e must not be too ready to dismiss a cause-and-effect hypothesis merely on the grounds that the observed association appears to be slight" (Bradford Hill, 1965). I view the strength of a perceived association not by magnitude, but by statistical significance, in determining causality (Fedak et al., 2015). Moreover, the consistency in the body of literature, another Bradford-Hill element, interplays with strength of association. If the strength of association is weak or moderate, but is statistically significant and appears consistently across numerous studies in different settings using different methods, then I will ascribe more weight to the strength of association element. Overall, I give significant weight to strength of association.

f. Temporality: Under the Bradford-Hill framework, temporality is required when examining whether exposure to a drug caused a disease. The exposure *must* precede the development of the disease. For this reason, I ascribe great weight to the element of temporality.

g. Specificity: Specificity is not an essential element for concluding that a causal relationship exists. Indeed, Bradford Hill instructed that "[w]e must not, however, over-emphasize the importance of this characteristic" (Bradford Hill, 1965). After

all, it has been argued that the causal association between smoking and lung cancer lacks specificity because smoking is associated with multiple other cancers. Still, should specificity exist, it is compelling evidence supporting causation. I ascribe mild weight to this element.

h. Experiment: While experimental evidence may provide strong support for causal inference, it may not always be possible to design an experiment to demonstrate a decreased risk of disease resulting from manipulation of an exposure. Additionally, ethical guidelines may preclude certain types of experiments, such as experiments involving exposures to a human fetus. In such cases, evidence from experimental studies in animal models may provide support for a causal association. Here, ethical guidelines have prevented human experiments to examine the relationship between prenatal APAP exposure and the development of neurodevelopmental disorders like ASD and ADHD. Even so, data from animal studies may provide support for causal association. In this context, I ascribe lesser weight to the experiment element. Also, information from treatment trials (with NAC) that target relevant conditions (such as ASD, ADHD, and impulse control disorders) as well as symptom domains (such as hyperactivity and impulsivity), and that inform underlying mechanism of action (such as oxidative stress), provide evidence in support of the element of experiment.

i. Analogy: While it can be helpful at times to compare the exposure at issue to others, this element is not necessary for a causation finding. Bradford Hill noted that "it would be fair to judge by analogy" only in "some circumstances." (Bradford-Hill, 1965). Thus, except in unusual circumstances where there is a directly analogous exposure, I place little weight on this element.

C. Strengths and Limitations of Bradford-Hill Framework

The Bradford-Hill approach is a generally accepted methodology in the field of epidemiology and has many notable strengths. First, the Bradford-Hill approach considers multiple factors, discussed above, which makes it comprehensive. Second, it provides for a structured, systematic method for assessing the causal association between an exposure and disease. Third, the Bradford-Hill approach, introduced in 1965, remains a widely-accepted, leading methodology for evaluating the causal association between an exposure and disease in the field of epidemiology.

However, the Bradford-Hill approach has some limitations. The framework cannot provide a definitive answer as to whether an exposure caused a disease based on the evidence. Additionally, the Bradford-Hill approach does not account for all confounding factors and cannot address all potential biases in study design. But considering numerous, well-designed epidemiological studies that control for confounding factors and account for potential bias can combat these limitations. Dr. Baccarelli uses a similar and equally accepted and reliable methodology, the Navigation Guide approach, in conjunction with the Bradford-Hill framework, to render his expert opinion in this litigation. Navigation Guide is a method to consistently evaluate the strength of individual articles, and the findings from such structured evaluations are used to inform the use of Bradford Hill factors in determining causation.

IV. The Weight of the Epidemiological Evidence Supports a Causal Association between Prenatal APAP Exposure and the Neurodevelopmental Disorders of ASD and ADHD in Offspring.

A. Literature Review

Weight of the evidence methodologies, including Bradford Hill analyses, require a review of the relevant scientific literature relating to the problem at hand; in this case, the relationship between prenatal APAP exposure and the risk of neurodevelopmental disorders, such as ADHD

and ASD, in offspring. To identify the relevant literature, I conducted searches on PubMed, an internet database of public scientific and medical research. My searches included the following search terms: acetaminophen, paracetamol, APAP, autism, ASD, attention-deficit/hyperactivity disorder ADHD, hyperactivity, and hyperkinetics. I reviewed the existing scientific research. Ultimately, I did not have sufficient time to complete a written analysis of each of the studies in sufficient detail. Accordingly, I have also relied upon the analysis and overall assessment of the epidemiology in Dr. Baccarelli's report. Below, I highlight some of the notable studies.

Baker et al. (2020) and Ji et al. (2020), both used biomarkers—rather than questionnaires—to measure APAP exposure. Baker et al. (2020) used meconium (or a newborn's first feces) to measure APAP exposure, whereas Ji et al. (2020) used umbilical cord blood to measure APAP exposure. Both biomarkers serve as a concrete measure of APAP exposure, which decreases the chance of misclassification bias due to reporting their APAP use incorrectly. Dr. Kolevzon suggests that these biomarkers only show peripartum exposure. (Kolevzon Report at 45). I respectfully disagree, as it is well documented that meconium is an accurate measure of exposure during the second and third trimesters. (Baker et al., 2020). As such, the biomarkers contribute to the validity of the studies. Using these concrete measures of APAP exposure, both Baker et al. (2020) and Ji et al. (2020) found significant increases in the odds ratio for ADHD and ASD. An increased odds ratio means that those children who were exposed to APAP had a higher chance of being diagnosed with ADHD or showing symptoms of ADHD than children who were not exposed. Additionally, Baker et al. (2020) had a long follow-up period and confirmed ADHD diagnoses with fMRI, which makes the results more reliable.

Another particularly strong study is Alemany et al. (2021), a collaborative study using the data from six European population-based birth cohorts. Impressively, this study included over

73,000 mother-child pairs and pooled the data, meaning that the data was analyzed independently by the authors rather than relying on the analysis of the cohort researchers. The mothers also reported medication use multiple times using standardized questionnaires, which decreases the chance of misclassification bias from mothers misreporting their APAP use due to issues with recall. From this exceptionally large group of participants, Alemany et al. found the data showed a consistent, positive association between prenatal APAP exposure and ADHD and ASD symptoms—a conclusion that several other authors of cohort studies and meta-analyses have reached. Dr. Kolevzon suggests that screening tools used in this study were overinclusive. (Kolevzon Report at 44). Even if this were true, this would not be expected to bias the results away from the null. Further, Appendix 3 of my Initial Report describes the reliability and validity of the scales utilized in this study. Additional assessment tools utilized in the relevant literature are described in the Appendix to this report. Further, the symptom domains measured by a well validated assessment tool are more sensitive and reliable than outcomes measured by a grouping of diagnostic criteria, whether in a clinical trial or in a birth cohort trial. I discuss the validity of these assessment tools in greater detail in Section V.A. of this report. Alemany et al. also found similar results when only examining those with hospital diagnoses of ASD and ADHD from the Danish National Birth Cohort (DNBC). The DNBC is one the world's largest birth cohorts with more than 180,000 participants with prospectively collected exposure data and biological samples that are linked at the individual level via unique ID numbers given to all citizens.

Additionally, several meta-analyses demonstrate a consistent, positive association between prenatal APAP exposure and ASD and/or ADHD symptoms and outcomes. A meta-analysis combines and analyzes results from multiple independent studies to give a better picture of the overall presence of a certain association. Meta-analyses are viewed as a higher quality of evidence

than a single original paper. Several high-quality meta-analyses, including Liew et al. (2014), Avella-Garcia et al., (2016), and Ystrom et al. (2017), show a positive association between prenatal APAP exposure and ASD and ADHD. Liew et al. (2014), for example, had several attributes contributing to the validity of the study, including controlling for several potential confounding factors. A confounding factor here is a feature that might be associated with APAP use and neurodevelopmental outcomes or symptoms (e.g., maternal age or maternal drinking). By controlling for multiple confounding factors, Liew et al. (2014) decreased the chance that in the study the observed association was due to something *other* than prenatal APAP exposure. Liew et al. (2014) also measured participants' symptoms using the Strengths and Difficulties Questionnaire (SDQ), a standard instrument that psychiatrists and psychologists use to assess and evaluate a patient's symptoms. The SDQ and other standard instruments used in these studies are frequently used in psychiatric assessments and evaluations and contribute to the studies' reliability.

Further, multiple strong studies also tested for a dose-response relationship, meaning that they explored whether ingesting more APAP during pregnancy increased the risk or severity of resultant ASD and/or ADHD symptoms or outcomes. Contrary to Dr. Faraone's conclusion that the studies do not show biological gradient, the two studies using a biomarker to measure APAP exposure, Baker et al. (2020) and Ji et al. (2020), *both* tested for and reported a positive dose-response relationship. This is significant because, as described above, biomarkers eliminate possible bias in determining level of APAP exposure. Other notable studies that tested for a dose-response relationship include Liew et al. (2014), Liew et al. (2016), and Ystrom et al. (2017). The presence of these dose-response relationships in multiple high-quality studies provides clear evidence of causation.

B. JJCI-Produced Documents Reviewed

I have reviewed the JJCI-produced documents available for Project Cocoon, including the Forest Plots that visually describe the findings of multiple studies of prenatal exposure to APAP and its association with ASD and ADHD/HKD behaviors and symptoms. These Forest Plots provide a comprehensive depiction of the strength and consistency of the studies discussed in this report as to the effects APAP has had on fetal brain development, which has caused life-long impairments to offspring of mothers taking APAP during pregnancy. Further, they highlight the transdiagnostic symptom domains that cut across ASD and ADHD that are most impacted by prenatal exposure to APAP (i.e., hyperactivity, emotion regulation difficulties, externalizing behaviors, and conduct problems). Since these company documents do not consist of any new or unknown primary evidence, I did not ascribe any additional weight to them.

C. A Bradford Hill Analysis Supports a Causal Association between Prenatal Use of APAP and Neurodevelopmental Disorders of ASD and ADHD.

I have performed the following analysis using the Bradford-Hill elements. As noted above, I rely on Dr. Baccarelli's comprehensive assessment of the relevant epidemiological literature to supplement my own review and understanding of the scientific evidence. As described below, the extensive number of epidemiological studies showing consistent, statistically significant associations between prenatal exposure of the fetus to APAP and the subsequent development of ASD and ADHD symptoms in offspring constitutes significant evidence of causation. Moreover, the evidence of dose response and plausible biological mechanisms weigh in favor of a causal association. Each of the Bradford-Hill elements is discussed below:

<u>Temporality:</u> Numerous studies in the epidemiologic literature on APAP and neurodevelopmental outcomes, including ASD and ADHD, have used a prospective cohort design (e.g., Baker et al., 2020; Ji et al., 2020; Brandlistuen et al., 2013; Liew et al., 2016). In this type of

study design, mothers are asked about their exposure to APAP during pregnancy, and the outcomes of interest, neurodevelopmental disorders, ASD, and/or ADHD, are then assessed months or years later. By definition, exposure to APAP precedes the development of these neurodevelopmental disorders. Thus, the temporality between prenatal APAP exposure and subsequent development of ASD and ADHD is satisfied under the Bradford-Hill framework and weighs in favor of causation.

Strength of Association: The literature reflects a consistent, statistically-significant association between prenatal APAP exposure and ASD and ADHD outcomes. While the association reported in the studies is moderate, they are statistically (and clinically) significant and stronger than other known causal associations. Importantly, the association between APAP exposure and ASD and ADHD has been found consistently in meta-analyses and systematic reviews (e.g., Masarwa et al., 2018; Gou et al.. 2019; Kim et al., 2020; Alemany et al., 2021; Ricci et al., 2023) weigh significantly in the analysis of literature when assessing causation. In addition, Bauer et al.'s consensus statement (2021) reported that a total of 29 observational studies conducted in 14 cohorts, involving over 220,000 mother-child pairs from various regions, had been conducted investigating the potential association between prenatal APAP exposure and neurodevelopmental outcomes. Among these studies, 26 out of 29 showed positive associations between the use of APAP during pregnancy and neurodevelopmental outcomes. When specifically examining studies focused on ADHD or ASD or both, out of 21 studies, 18 found a positive association between prenatal APAP exposure and these conditions (e.g., Baker et al., 2020; Ji et al., 2020). Moreover, JJCI's Forest Plots depict the strength and consistency of these associations. This element is satisfied under the Bradford-Hill framework and weighs in favor of causation.

Consistency: Numerous studies conducted over the past 15 years, including meta-analyses (e.g., Ricci et al., 2023; Gou et al., 2019; Masarwa et al., 2018), pooled analyses, and individual

cohort studies, consistently demonstrate an association between prenatal APAP exposure and ASD and ADHD. Taken together, the consistency across the epidemiological literature provides strong evidence for causality. For example, Bauer's consensus statement identified 21 studies on prenatal APAP exposure and a potential association with ASD and/or ADHD, 18 of which showed a positive relationship between prenatal APAP exposure and ASD and/or ADHD (Bauer et al., 2021). The research was conducted in large prospective studies, comprising comprehensive pregnancy and birth cohorts from multiple countries and time periods and conducted by multiple research groups. These studies utilized various exposure and outcome measures, demonstrated dose-response relationships, and accounted for potential bias and confounding. Even unique study designs and data collection methods, like those used in Bauer & Kriebel (2013) resulted in similar findings, bolstering the overall consistency of the association. Although there are some null studies, those studies are in the minority and are greatly outnumbered by the studies that did find a statistically significant association. As such, these results satisfy the consistency element in the Bradford-Hill framework, and this factor weighs in favor of causation.

<u>Plausibility:</u> There are multiple plausible mechanisms of action to explain the association between prenatal APAP exposure and the development of ASD and ADHD symptoms in children. As more thoroughly explained in Section V.E and in the reports of Drs. Pearson and Cabrera, these mechanisms include (1) APAP's tendency to lead to excess NAPQI formation; (2) APAP's ability to cause oxidative stress; (3) APAP's effects on the prostaglandin system; (4) APAP's ability to disrupt the endocannabinoid system; (5) APAP's ability to disrupt the endocrine system; (6) APAP's effect on BDNF levels; and (7) APAP's ability to cause epigenetic changes. Thus, there is substantial evidence of a biologically plausible mechanism for prenatal APAP exposure to cause ASD and ADHD in offspring. This factor weighs in favor of causation.

Coherence: The element of coherence requires that "the cause-and-effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease" (Bradford Hill, 1965). Hill uses the example of lung cancer and comments that its association with cigarette smoking is coherent with the increase in lung cancer over time. In this case, the body of epidemiological evidence on prenatal exposure to APAP is coherent with the repeated observed associations with the increased risk of development of ASD and ADHD symptoms and outcomes. As explained in my Initial Report, the fetal brain is particularly susceptible to environmental insults during development, and environmental factors like pharmaceuticals. The ecological evidence also supports coherence, as increases in APAP use in the 1980s has been found to correlate with increasing rates of ASD in California, but cessation of APAP use resulted in a plateau effect in California in the rates of ASD (Becker & Schultz, 2010). The body of evidence strongly supports a causal association between prenatal APAP exposure and the subsequent development of ASD and/or ADHD in offspring.

Biological Gradient (Dose Response): A biological gradient, or dose-response relationship, refers to the observation that the greater the exposure to a risk factor, the greater the risk of developing the outcome (e.g., a disease or other adverse health outcome). A dose-response relationship is strong evidence of a causal relationship between the exposure and the outcome. In fact, it is difficult to account for the presence of a dose-response relationship without looking to causation. My literature search produced six studies that assessed dose response for ADHD (Liew et al., 2014; Avella-Garcia et al., 2016; Liew et al., 2016; Ystrom et al., 2017; Baker et al., 2020; Ji et al., 2020) and two studies that assessed dose response for ASD (Liew et al., 2016; Ji et al., 2020). Significantly, a dose-response relationship has been found in the studies that have used concrete measurements of APAP in biomarkers, cord plasma and meconium, as opposed to

maternal self-report, to assess exposure. Ji, et al. found that prenatal APAP exposure was associated with a "significantly increased risk of ADHD and ASD in a dose-response fashion" (Ji et al., 2020). The authors analyzed the data in tertiles, where the data set was arranged in order by values then divided into three groups, with each group containing one-third of the data. The cord APAP burden was calculated by measuring the level of unchanged acetaminophen and known acetaminophen metabolites in the cord blood and adjusting for fetal metabolic conditions using known metabolite proportions from the adult acetaminophen pathway. Compared to the first tertile, the second tertile was associated with 126% higher odds of ADHD diagnosis, and the third tertile was associated with 186% higher odds of ADHD diagnosis. The observed dose-response relationship was even more pronounced for ASD diagnosis, where the third tertile was associated with an associated with 262% higher odds of ASD diagnosis compared with the first tertile. Additionally, Baker et al., which used meconium as a biomarker of APAP exposure, identified a linear dose-response relationship based on increases in prenatal APAP exposure and ADHD (i.e., each doubling of prenatal APAP exposure increased the odds of ADHD by 10% (OR, 1.10; 95% CI, 1.02-1.19)) (Baker et al., 2020). Bradford Hill views this linear dose response as compelling, as "the fact that the death rate from cancer of the lung rises linearly with the number of cigarettes smoked daily, adds a very great deal to the simpler evidence that cigarette smokers have a higher death rate than non-smokers" (Bradford Hill, 1965). In Liew et al. (2016), "dose-response patterns" were seen with increased duration of use throughout the pregnancy and ASD risk (P-trend = 0.006 and P-trend = 0.052 for ASD and infantile autism, respectively). Additionally, for ADHD, a dose response was observed with longer duration of APAP use and more frequent APAP use (e.g., Liew et al., 2014; Avella-Garcia et al., 2016; Ystrom et al., 2017). In each of these studies, as the prenatal APAP exposure increased, so too did the risk of the offspring developing ASD and/or ADHD.

Because a dose response was identified between prenatal APAP exposure and ASD and/or ADHD in these studies that evaluated a dose response, I find that this Bradford-Hill element is met and weighs in favor of causation.

Specificity: Although numerous studies have found a positive association between prenatal APAP exposure and ASD and ADHD in offspring, I do not find that the association meets the specificity element under the Bradford-Hill framework. That is, while the epidemiological literature includes multiples studies showing an association between prenatal APAP use and ASD and ADHD, the association of prenatal APAP use is not limited to those conditions. Based on my analysis, the element of specificity is not satisfied. However, as specificity is but one element in the Bradford-Hill framework, this does not preclude a finding of causation in this case.

Experiment: Although experimentation can be a compelling factor for supporting an argument of causality, ethical considerations prevent randomized controlled trials in humans to investigate the association between prenatal APAP exposure in humans and neurodevelopmental disorders like ASD and ADHD. Bradford Hill comments that "it is possible to appeal to experimental, or *semi-experimental*, evidence" to support an observed association (Bradford Hill, 1965) (emphasis added). Hill gives the example of reducing dust in a workshop or ceasing smoking cigarettes, then asking whether the frequency of the associated event is affected. By Hill's definition, it is arguable that ecological data on trends in APAP use and ASD satisfy this element. As discussed above, following the cyanide-laced APAP deaths in the 1980s, APAP use decreased and the rates of ASD plateaued and slightly decreased (Becker & Schultz, 2010). The study showing the disparity in ASD rates in the United States compared to Cuba, which tracks APAP use, also tends to show that decreased APAP use in a population corresponds to a lower rate of

ASD. As Fedak et al. (2015) notes, however, a modern application of Hill's "experiment" element includes toxicological findings, in vitro studies, and animal models.

Also, there is evidence from animal models that prenatal (and perinatal) APAP exposure can cause neurodevelopmental symptoms in rodents that are characteristic of specific overlapping features of ASD and ADHD. The reports of Dr. Pearson and Dr. Cabrera describe these studies from animal models, and their strengths and weaknesses. For instance, Klein et al. conducted a study where Wistar rats were force-fed APAP (350 mg/kg/day) or water from gestational day 6 until delivery (Klein et al., 2020). The gestational exposure to APAP resulted in impaired nest-seeking behavior, increased apomorphine-induced behavioral stereotypy, and decreased rostral grooming in the rats. Another study by Blecharz-Klin revealed significant changes in serotonergic and dopaminergic neurotransmission in the prefrontal cortex and striatum of APAP-exposed rats, along with effects on spatial memory and exploratory behavior (Blecharz-Klin, 2017). In a subsequent study, the same research group found that daily administration of 5 mg/kg or 15 mg/kg of paracetamol (APAP) to pregnant rats led to a nearly twofold decrease in brain-derived neurotrophic factor (BDNF) levels in the prefrontal cortex, hippocampus, and striatum of the exposed animals (Blecharz-Klin, 2018). Additionally, these exposed rats exhibited a lower frequency of social interactions and social sniffing compared to the control group. Overall, rodent studies have consistently aligned with epidemiological data supporting a causal association between prenatal APAP exposure and neurodevelopmental disorders in offspring. Finally, exposure to APAP causes epigenetic activation of 92 autism-linked genes (Carter & Blizzard, 2016), which is the greatest of any substance other than valproate, which is known to cause ASD. Thus, this Bradford-Hill element is satisfied and weighs in favor of causation.

Analogy: The analogy element in the Bradford-Hill framework looks to whether another type of exposure leads an analogous medical outcome. Bradford Hill comments that "[w]ith the effects of thalidomide and rubella before us we would surely be ready to accept *slighter but similar* evidence with another drug or another viral disease in pregnancy" (Bradford Hill, 1965) (emphasis added). The element has been interpreted as meaning that "one causal agent is known, the standards of evidence are lowered for a second causal agent that is similar in some way" (Fedak, et al., 2015). As discussed above, prenatal exposure to valproic acid is associated with an increased risk of autism and neurodevelopmental outcomes in offspring (Christensen et al., 2013; Christensen, et al., 2019). In fact, the label for valproic acid warns that observations studies have shown "exposure to valproate products during pregnancy may increase the risk of autism spectrum disorders" and "the weight of the evidence supports a causal association between valproate exposure in utero and subsequent adverse effects on cognitive development."[1] While I do not consider this Bradford-Hill element essential, I find that it is met in the present case.

Based on my review of the Bradford-Hill elements, I conclude that prenatal exposure to APAP can cause ASD and ADHD in offspring.

D. Critique of Dr. Kolevzon's and Dr. Faraone's Bradford Hill Analyses

Neither Dr. Kolevzon nor Dr. Faraone properly perform a Bradford Hill analysis. Dr. Kolevzon failed to examine all relevant scientific evidence before concluding that "the absence of a statistically significant association" means that "a causality analysis using traditional methods, such as the Bradford Hill criteria, is not warranted." (Kolevzon Report at 43). He claims that

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[1] Label for Depakene (Valproic Acid), https://www.accessdata.fda.gov/ drugsatfda_docs/label/ 2016/018081s065_018082s048lbl.pdf/ (last accessed June 15, 2023).

studies that use measures of ASD other than physician diagnosis are not germane to the causation analysis. As I explain further in Section V of this rebuttal report, the literature utilizing outcome data derived from vetted and approved diagnostic tools like questionnaires and assessments is valuable to a causation analysis. The studies that use such tools should be included in any weight-of-the-evidence methodology. If Dr. Kolevzon had considered all of the relevant scientific evidence, he would not have been able to conclude that there was no statistically significant association between prenatal APAP exposure and ASD in offspring. An analysis that that just focuses on a select few reports that support a conclusion and that summarily rejects an enormous body of relevant evidence is methodologically flawed. A results-driven analysis that declines to apply the Bradford Hill analysis or any scientific weight of the evidence methodology is not valid.

Dr. Faraone concluded that none of the Bradford Hill criteria support causation. He suggests that the scientific literature does not show a statistically significant association because some studies do not control for genetic confounders. But Dr. Baccarelli's report details how some of the epidemiology studies have indeed controlled for genetic confounders and still demonstrate statistically significant association for APAP exposure and ASD, ADHD, and neurodevelopmental disorders. In addition, Dr. Baccarelli and Dr. Cabrera have described how sibling pair studies would mask or understate a true association when, as here, genetic and family factors are mediators or modifiers of the effects of APAP.

In addition, Dr. Faraone concludes the specificity element is not satisfied because studies that consider different or non-specific neurodevelopmental disorders are not relevant to whether prenatal APAP exposure causes ADHD. To the contrary, as I have discussed in great detail in my Initial Report, it is widely accepted that neurodevelopmental disorders including ASD and ADHD share important neural, genetic, physiological, structural, and psychological traits (Barch, 2020).

As a result, studies that utilize neurodevelopmental disorder outcomes can provide insight to the specific causation question relating to ASD and ADHD. Dr. Faraone also concludes the plausibility criterion is not satisfied because there is “no definitive description of any pathologic mechanism that explains the onset and symptoms of ADHD.” (Faraone Report at 100). Based on my familiarity with the Bradford Hill framework, the plausibility element is satisfied even if the mechanism cannot be or has not been conclusively proven. The mechanisms described in my initial report and in Dr. Cabrera’s report are certainly plausible, and thus satisfy this factor.

V. ADDITIONAL RESPONSES TO DEFENDANTS’ EXPERT REPORTS

Defendants’ experts raised several specific critiques of my Initial Report. As noted above, my Initial Report, as well as the expert reports of Dr. Baccarelli, Dr. Cabrera, Dr. Louie, and Dr. Pearson, provide analyses that rebut these critiques. While my rebuttal report is not intended to address every critique provided by the Defendant’s experts, I provide additional responses to certain critiques below.

A. Surveys in Lieu of Clinical Diagnoses

In his report, Dr. Faraone states that “[w]hile Dr. Baccarelli is correct that a diagnosis of ADHD is performed by a healthcare provider, his statement ignores the fact that most of the studies at issue did not use healthcare provider diagnoses. The studies instead used proxies based on questionnaires that were generally not filled out by a health care professional but rather by a parent or teacher. Even when a diagnosis is made by a health care provider, the report made by the mother can still be biased regardless of whether the health care provider knows about the parent’s use of acetaminophen. The Masarwa 2020 meta-analysis showed that non-differential misclassification can bias risk ratios away from the null.” (Faraone Report at 67).

Dr. Faraone's position is contrary to multiple, peer-reviewed studies validating use of questionnaires in a research setting. The use of caregiver-reported questionnaires in lieu of clinical diagnoses via healthcare professionals is a frequently used and well-validated method of research; and the assessments discussed in my report have been examined in their ability to accurately diagnose/screen for ASD and ADHD in multiple studies. The body of epidemiology which forms the basis of my opinion and the opinion of Dr. Baccarelli uses well validated methods as proxies for a diagnosis of ADHD and ASD as well as, in some cases, medical records with diagnostic codes and medical examination. Some studies which focus on other neurodevelopmental outcomes may use equally well validated methods to identify symptomology consistent with neurological damage, including ADHD and ASD.

Validation studies have shown the Developmental and Well-Being Assessment (DAWBA) to be a good measure for both epidemiological studies and in clinic assessments. DAWBA has been shown to be an accurate and sufficient measure to assess for ADHD in clinical community settings, without direct patient contact by the diagnosing clinician (Foreman et al., 2009), and has good agreement with the Autism Diagnostic Interview–Revised (ADI-R), a gold standard diagnostic caregiver interview used to diagnose ASD (Murphy et al., 2018). Most importantly, this questionnaire can be completed without direct patient contact, making it ideal for community settings and large-scale epidemiological studies. The Child Behavior Checklist (CBCL) 1½ to 5 years parent/caregiver and teacher forms DSM-ASD (previously DSM-pervasive developmental problems, DSM-PDD) subscale has been validated as a good Level 1 screener of ASD with good discriminatory questions and measurement invariance across multiple diverse populations (Levy et al., 2019; International ASEBA Consortium et al., 2020). Research supporting its use as a screening measure for ASD include studies conducted by the Study to Explore Early Development,

a multi-site case control study that included well-established ASD research centers including the CDC, Kaiser Permanente, the Children's Hospital of Philadelphia and Kennedy Krieger. The CBCL had a sensitivity of over 80% for ASD, with specificity ranging from 0.5 (developmental delay with ASD features) to 0.93 (population controls). One of the strengths noted by the authors is the ability to use it without a healthcare professional being present (Levy et al., 2019). Although ASD is not included in the syndrome scales for school-age children, the CBCL 6 to 18 years parent/caregiver and teacher forms have also been validated as appropriate screeners for ASD when examining scores on specific subscales, including the Thought and Social Problems scales (Mazefsky et al., 2011), and the Withdrawn/Depressed, Social Problems and Attention Problems scales (Arias et al., 2022). The CBCL DSM-oriented subscale for ADHD and the Attention Problems subscale have both been validated as diagnostic measures and screeners for ADHD, with good predictability for later diagnoses of the disorder (Biederman et al., 2021; Oerbeck et al., 2020; Spencer et al., 2018). Additionally, validity and test-retest reliability has been examined in multiple large population-based observational studies for the Childhood Autism Spectrum Test (CAST) that include samples from general populations of school-aged children. It shows good sensitivity and specificity for autism spectrum symptoms with a moderate positive predictive value. A cut-off point of 15 has been used; at this level there is a sensitivity of 100%, specificity of 50%, and positive predictive value of 50% (*The Childhood Asperger Syndrome Test (CAST)*, n.d.; J. Williams et al., 2005, 2006; J. G. Williams et al., 2008).

The Conners Parent Rating Scale- Revised short form (CPRS-R:S) is useful for the assessment of children and adolescents with ADHD, as it assesses the 12 criteria listed in the DSM-IV for ADHD (Kumar & Steer, 2003). The ratings are summed to yield a 6-item oppositional, 6-item cognitive problems/inattention and 6-item hyperactivity scale. It also includes the ADHD

Index, which includes items found to best discriminate youth with ADHD from neurotypical peers. The Conners rating scale system was revised as the Conners-3 in 2008 (*Conners 3rd Edition*, n.d.). In addition, the Conners Kiddie Continuous Performance Test (Conners K-CPT) is frequently used in epidemiological and clinical research, and the variables have been correlated to ADHD symptoms (Epstein et al., 2003; Conners et al., 2003; Breaux et al., 2016).

The Strengths and Difficulties Questionnaire (SDQ) is shown to be a valid tool for discriminating cases with ADHD from those without ADHD or with other mental health diagnoses in large population-based studies, including those that had confirmed diagnoses via a medical/healthcare professional (Algorta et al., 2016; Russell et al., 2013). It has also been studied in ASD populations and in individuals with co-morbid ASD and ADHD, with good sensitivity and specificity reported (Riglin et al., 2021; Overgaard et al., 2019). The DSM-ADHD Questionnaire, and related nosology measures, has been validated as a way to differentiate symptoms and diagnose preschoolers, in addition to older children and adults (Sterba et al., 2007).

Next, Dr. Kolevzon states: "In his report, Dr. Hollander states that 'it is appropriate to review the body of evidence that measures neurodevelopmental disorders and to not limit the analysis to studies that focus on ASD and ADHD as specified outcomes.' Epidemiological studies that use scores or ratings from various non-specific instruments cannot reliably demonstrate an association between maternal acetaminophen use during pregnancy and the development of ASD in offspring. As I have discussed, screening tools or related clinical outcome assessments are not proper proxies for a clinical diagnosis of ASD because the symptoms they test are mostly non-specific to ASD and could have different explanations or causes." (Kolevzon Report at 62).

In my Initial Report, I explained that an investigation of whether prenatal APAP use can cause neurodevelopmental disorders of ASD and ADHD necessarily includes looking to the full

body of literature on neurodevelopmental disorders. (Hollander Amended Report at 86). And, as discussed above, numerous validation studies have shown that "screening tools or related clinical outcome assessments" are valid ways of assessing ASD.

Additionally, several large, reputable registries have examined whether screening tools are valid, reliable ways to assess outcomes. For instance, the DNBC is one the world's largest birth cohorts with more than 180,000 participants with prospectively collected exposure data and biological samples that are linked at the individual level via unique ID numbers given to all citizens.[2] Large registries, like the DNBC, are frequently examined in validation studies to confirm the accuracy of the reported diagnoses, and over 90% of ASD diagnoses have been confirmed in the majority of these databases (Lauritsen et al., 2010; Lampi et al., 2010; Idring et al., 2012; Fombonne et al., 2004; Hagberg & Jick, 2017). Newly-developed databases often rely upon parent/caregiver affirmations of ASD diagnoses, or on self-declarations of independent adults with ASD. No proof of professional ASD diagnosis is required upon registration in these registries. This includes the Interactive Autism Network (IAN), and its successor, the Simons Powering Autism Research and Knowledge (SPARK) database. SPARK recruits participants with an ASD diagnosis from a physician, psychologist, school, or therapist; but does not independently verify these diagnoses with supporting documentation. Registrants also complete multiple questionnaires that assess target symptoms in ASD. Strong evidence of the validity of the ASD diagnoses in the SPARK cohort has been found when confirmed via record and EMR (electronic medical record) review. (Fombonne et al., 2022). It is important to note is Fombonne's acknowledgement that

[2] About the DNBC, https://www.dnbc.dk/about-the-dnbc (last accessed July 27, 2023).

SPARK caregivers reports on their offspring are based on observations they have made over time and across multiple contexts, while medical reports from EMRs only summarize history and observation data from one point in time. This supports the use of caregiver reports of ASD/ADHD symptoms in epidemiological studies, in addition to that of registry data. Additionally, Dr. Kolevzon has utilized the SPARK database in his research—***without*** independently confirming the caregiver reported ASD diagnoses in a study on comorbidities in ASD. (Khachadourian et al., 2023).

Further, Eric Fombonne et al. describe the validity of such approaches. (Fombonne et al., 2022). The SPARK cohort was established to facilitate recruitment in studies of large numbers of participants with autism spectrum disorder (ASD). Online registration requires participants to have received a lifetime professional diagnosis by health or school providers although diagnoses are not independently verified. This study was set to examine the validity of self and caregiver-reported autism diagnoses. Electronic medical records (EMR) of 254 SPARK participants. Using two different methods, confirmation of ASD diagnosis in EMRs was obtained in **98.8% of cases**. Core clinical features recorded in EMRs were typical of autism samples and showed very good agreement with SPARK cohort data, providing further evidence of the validity of clinical information in the SPARK database. Parent and scale-diagnoses are very similar (98%) to clinician diagnoses.

In sum, the well-studied and validated questionnaires and assessments referenced in my report and used in the epidemiological literature are highly similar to diagnoses by healthcare professionals, and may be more sensitive and accurate reflections of the symptom domains within a neurodevelopmental disorder than the DSM diagnostic criteria.

B. Validity of Animal Studies

Dr. Faraone states: “Several plaintiff experts, including Drs. Cabrera, Pearson and Hollander, rely on rodent studies as supposed evidence of a causal link between exposure to acetaminophen and the development of ADHD. While such studies are valuable for generating hypotheses, observing the behavior of rodents exposed to acetaminophen—an entirely different species that has different and significantly more limited neurological and psychological capacities than humans—cannot explain the effect of acetaminophen exposures on the human brain or human behavior. The rodent studies on which plaintiff experts rely—a number of which involve direct, as opposed to in utero, exposures to acetaminophen—do not address behaviors relevant to the diagnostic criteria for ADHD, and in some cases, address behaviors and neurological effects that have no connection to any ADHD symptom.” (Faraone Report at 76).

Similarly, Dr. Faraone states: “Finally, rodent studies have not been successful in developing new treatments or diagnostic methods or ADHD or, for that matter, any clinically actionable event that is useful in the management of ADHD, raising serious questions about their usefulness in this context. To the contrary, rodent studies have impeded the treatment of ADHD, with studies of the medications for ADHD inaccurately concluding that those medications would lead to addiction in ADHD youth treated with those medications.” (Faraone Report at 90).

I respectfully disagree. Dr. Faraone questions the use of animal models as causal evidence for neurotoxic exposures. While limitations to animal models are acknowledged, they are necessary to understand the underlying biology of ASD, ADHD, and related disorders, and to aid in the development and testing of therapeutic agents, just as they are used in other disorders including Alzheimer’s, schizophrenia and Huntington’s disease. ADHD is a multifactor model due to the known interaction between the genetic causes and environmental factors in its causation, and the animal models used must consider all of these factors to test for interactions. While no

existing rodent model captures all aspects of ADHD, several represent the different symptom domains of ADHD. Although ADHD's complexity makes developing preclinical animal models challenging, researchers note that animal models can help to isolate characteristic symptoms of ADHD and trace these at a cellular/molecular level, and contribute to the understanding of the neurochemical, neuropathological, genetic and environmental factors of ADHD. Rodent studies are noted to be preferable and useful for both understanding the mechanisms and developing treatments. Further, in response to Dr. Faraone's statement about animal models failing to lead to treatment developments, it is clear that genetic studies of ADHD (and ASD) have failed to lead to new treatment developments.

C. Validity of the Transdiagnostic Approach

Dr. Faraone states: "Plaintiffs' expert Dr. Hollander uses a 'transdiagnostic approach' that improperly considers various neurodevelopmental disorders—including ADHD and autism spectrum disorder (ASD)—as if they were a single disorder. He asserts that 'when analyzing causal associations between a toxic exposure and neurodevelopmental disorders such as ASD and ADHD, it is appropriate to consider comprehensive evidence that examines a variety of neurodevelopmental symptoms.' Dr. Hollander also characterizes the distinctions between ASD and ADHD as 'artificial' and states that 'ASD and ADHD share important neural, genetic, physiological, structural, and psychological traits.'" (Faraone Report at 34). Dr. Faraone further states: "The diagnostic criteria for ADHD and ASD have been validated by decades of research, including in DSM field trials. The criteria are very different for each disorder. None of the behavioral diagnostic criteria of one disorder are included as behavioral diagnostic criteria for the other disorder in either the DSM or ICD. These diagnostic criteria have been shown to be clinically useful categories that predict course, outcome, response to treatment, and family history, which

are the appropriate bases for validating diagnostic boundaries. I have used the diagnostic criteria to validate the diagnosis of ADHD in my research." (Faraone Report at 34).

I disagree with Dr. Faraone's position. The DSM-5 diagnostic approach has attempted to incorporate genetic and environmental factors into diagnostic criteria, but to date this approach has been unsuccessful. As a result, as demonstrated in my Initial Report, an alternative transdiagnostic RDOC approach has been utilized by the National Institutes of Health (NIH) since it is more representative of and sensitive to integrating environmental, genetic, imaging and biomarker measures, as well as neural, genetic, physiological, structural, and psychological traits.

D. Criticism that Mechanism Does Not Link to ASD and ADHD

Dr. Powell states, "Dr. Hollander asserts in his report that he 'reviewed the scientific evidence to assess whether there was a plausible biological mechanism by which prenatal use of APAP could impact fetal brain development and cause neurodevelopmental disorders.' But even if Dr. Hollander were correct that prenatal acetaminophen could impact or lead to changes in the developing fetal brain, he lacks any reliable scientific evidence that those changes have any relationship to ASD or ADHD, which are the relevant outcomes at issue in this litigation. Dr. Hollander essentially takes the position that any change in the brain during or following prenatal exposure to acetaminophen provides evidence of a mechanism by which prenatal acetaminophen exposure causes ASD and/or ADHD. As a result, Dr. Hollander relies on literature purporting to connect acetaminophen exposure with certain physiological brain characteristics or human behaviors, rather than a clinical diagnosis of ASD and ADHD, as evidence of a mechanism. This approach is contrary to good science. When considering whether there is an association between a drug and a particular diagnosis, non-diagnostic characteristics such as behavioral symptoms are not sufficient to establish a causal link between the drug and the particular diagnosis. In other

words, if children who were exposed to acetaminophen during fetal development are statistically significantly more active than children who were not, but this difference does not reach the level of a neuropsychiatric diagnosis of the particular condition being investigated, then the difference cannot support the conclusion that acetaminophen exposure causes that condition." (Powell Report at 95).

I respectfully disagree. Dr. Powell incorrectly takes the unsupportable position that a study must reach the outcome of ASD or ADHD in order to be relevant to the overall question of whether APAP exposure during neurodevelopment causes ASD or ADHD. But, as Dr. Pearson notes in his rebuttal report, "[s]ince different functional domains are evaluated by different tests in the study, a complete concordance of effects is not expected and/or necessary to establish the relevance and/or validity of a finding." (Tyl et al., 2008; *see* Pearson Rebuttal Report at 4).

Here, hyperactivity is a symptom domain that is a core feature of ADHD and an associated symptom domain of ASD. If acetaminophen exposure during pregnancy causes hyperactivity in ASD and ADHD individuals, and if hyperactivity is a common feature of ADHD and ASD, then acetaminophen causes ADHD and ASD. Treatments that are developed for ADHD and ASD do not treat all the different symptom domains of ASD and ADHD, but rather one symptom domain within the condition. For example, risperidone treats irritability and disruptive behaviors in children with ASD. This treatment is approved by the FDA for the treatment of the symptom domain of disruptive behaviors and irritability in ASD. If the treatment successfully treats a symptom domain within a condition, then the regulatory bodies would approve the treatment for the symptom domain within the condition, and not require that the treatment treat all the various symptom domains in that condition.

E. Polanczyk and ADHD Prevalence Over Time

Dr. Faraone asserts that "Plaintiffs' experts do not acknowledge the data from Polanczyk et al. (2014) showing the stability of ADHD's true prevalence over time" (Faraone Report at 18).

While Dr. Faraone notes that I did not acknowledge the data from Polanczyk et al., 2014, this is incorrect. In Section C of my Initial Report, I state the following: "Community samples of children and adolescents from 35 countries in six continents show a prevalence rate of ADHD ranging from 5% to 29% (Polanczyk et al., 2014). Meta-analyses of studies from these countries suggest that when the study methods used are consistent, there are no temporal changes in the number or severity of symptoms, and worldwide prevalence rates have been stable across time (1985 to 2012)." (Hollander Report at 39). However, I further note and clarify that "[w]ithin North America, the National Survey of Children's Health (NSCH) regularly completes population-based surveys examining prevalence rates of multiple neurodevelopmental, mental health, and medical disorders in addition to other aspects of children's health. Through this study, the percentage of children with a lifetime diagnosis of ADHD increased from 7.8% to 9.5% from 2003 to 2007, a 21.8% increase. From 2003 to 2011, NSCH determined that the number of children aged 3 to 17 ever diagnosed with ADHD in the US steadily increased from 4.4 million to 6.4 million. Prevalence estimates from 2016 to 2019 show that 6 million children in the US aged 3 to 17 were ever diagnosed with ADHD. Additional studies of ADHD medication usage have demonstrated that 66.3% of children and adolescents with a current ADHD diagnosis were taking medication for the disorder, which represented 4.8% of all children aged 4 to 17 years. In California, an analysis of medical records from 2001 to 2010 showed a relative increase of 24% in the incidence of physician-diagnosed ADHD in children aged 5 to 11 (Getahun et al., 2013). These numbers are consistent with other studies that use administrative data to calculate prevalence rates in the USA,

UK, and Canada from 1990s through 2000s (Bitsko et al., 2022; Cree et al., 2023; Danielson et al., 2018; G. Polanczyk et al., 2007; G. V. Polanczyk et al., 2014; Posner et al., 2020; Visser et al., 2016)."

F. Claim that Reliance on Gervin Study Is Flawed

Dr. Faraone states: "While Dr. Hollander notes that one study found that acetaminophen caused epigenetic changes in cord blood that involved genes regulating oxidative stress, that study did not show that those changes led to subsequent ADHD." (Faraone Report at 93).

Respectfully, this criticism is not well taken. As I note above, for a study to be relevant to causation of ADHD, it need not have an ADHD diagnosis as an endpoint in the study. Research that addresses one of the links in the mechanism of action that starts with acetaminophen exposure and results in ADHD can provide valuable insights into causation. Demonstrating that acetaminophen caused epigenetic changes to genes that regulate oxidative stress is an important link in one of the primary mechanisms of action for acetaminophen. For example, as Dr. Cabrera points out, the link between a chemical exposure and oxidative stress is one of the Key Events identified in published Adverse Outcome Pathway 20. (Cabrera Report at 36-37). Acetaminophen is one of the identified stressor chemicals for AOP 20. *Id*. And AOP 20 demonstrates that exposure to these chemicals during "brain development" may create "oxidative stress" sufficient to "cause cellular injury and death" that disrupts "the establishment of neuronal connections and networks" and can "lead to functional impairment in learning and memory." (Cabrera Report at 36).

I note that Dr. Faraone does not dispute the findings of the Gervin study that acetaminophen causes epigenetic changes in genes that regulate oxidative stress. These findings are a concrete demonstration of the interaction of acetaminophen with genetic factors. Furthermore, the findings of Gervin combine with a large body of studies to demonstrate the causal link from acetaminophen

to ADHD and ASD, as I described in the section of my Initial Report discussing the plausible mechanisms of action. Dr. Cabrera also sets forth substantial evidence supporting the entire chain that links acetaminophen to oxidative stress to neurodevelopmental disruption to neurodevelopmental disease including ADHD and ASD. (Cabrera Report at 39-129). This evidence includes studies demonstrating that APAP at therapeutic doses generate sufficient NAPQI to cause significant oxidative stress (Cabrera Report at 62-64), that APAP readily crosses the placenta and bypasses the fetal liver and is shunted to the developing fetal brain (Cabrera Report at 59), that APAP concentrations may be two to seven times higher in developing fetal brains compared to adult brains (Cabrera Report at 59-60), that all relevant brain tissues and brain capillaries produce the enzyme that results in the toxic metabolite NAPQI (Cabrera Report at 60-61), that NAPQI exerts oxidative stress and depletes glutathione in the brain even at relatively low doses (Cabrera Report at 66), that the developing brain has lower levels of protective glutathione (GSH) than the adult brain (Cabrera Report at 65), and that autism is linked to lower levels of glutathione (GSH) and increased levels of oxidized glutathione (GSG) (Cabrera Report at 65).

G. Claim that Carey Study Was Not Addressed

In his report, Dr. Powell states: "First, in discussing the NAPQI/oxidative stress theory, neither Dr. Hollander nor Dr. Baccarelli cites any studies demonstrating that increased biomarkers of oxidative stress during gestation are associated with increased ADHD or ASD clinical diagnoses. Instead, Dr. Hollander cites Rommel 2020 as reporting a correlation between oxidative stress markers in maternal urine and behavioral traits (but not clinical diagnoses) for ASD. But Carey 2022, the only other human study designed to assess the link between increased biomarkers of oxidative stress during gestation and autism-related disorders, did not replicate these findings. To the contrary, as explained above, Carey 2022 found that increased oxidative stress is not

associated with increased autism-related outcomes. As a result, when considered together, these studies do not support the assertion that oxidative stress is a plausible biological mechanism by which prenatal acetaminophen exposure causes ASD (or ADHD) as diagnosed clinically" (Powell Report at 97).

Again, Dr. Powell takes the position that a mechanism study is not relevant if it does not use ASD or ADHD diagnosis as an endpoint. As noted above, a study investigating a biological mechanism, such as oxidative stress, may provide valuable information on causation even if its endpoint is not an ASD or ADHD diagnosis. Furthermore, Carey (2022), which is discussed in my Initial Report, did find that, before adjustment, there was a statistically significant association between oxidized glutathione and ASD (OR2.27, 95% CI 1.07, 4.81). After adjustments, the association still had an OR above 2.0, but it lost statistical significance (95% CI 0.89, 4.62). That the study was under-powered to reach statistical significance does not imply a finding that maternal oxidative stress has no effect on ASD. In addition, Anand (2021), a prospective cohort study of over 3,000 mother-child pairs followed from 1998 to 2018, concluded that APAP concentrations in cord blood above the 50th percentile were associated with an ADHD diagnosis (OR: 2.10, 95% CI 1.43, 3.11), and a marker of oxidative stress in cord plasma was likewise associated with higher odds of ADHD.

H. Claim that Rare Genes Are Penetrant

In her report, Dr. Chung claims "Dr. Hollander and Dr. Baccarelli's reports attempt to diminish the role of genetics in the etiology of ASD and ADHD. In his report, Dr. Hollander acknowledges that 'genes account for up to about 85 percent of autism's heritability' (Dr. Hollander Amended Report, p. 18). However, he then writes that 'only about 10 percent of individuals with ASD have an identifiable genetic cause' (Dr. Hollander Amended Report, p. 18).

Dr. Baccarelli also acknowledges that 'more than 800 genes' are currently found associated with ASD, but then states 'no single genetic etiology accounts for more than 0.2% of cases among individuals with nonsyndromic ASD' (Dr. Baccarelli Amended Report, p. 42). Although we do not yet know the full architecture of genetics and thus do not yet know all the genes or genetic variants and their roles in ASD and ADHD, it is well established that genetics play a critical role in causing these conditions. Drs. Hollanders and Baccarelli neglect to acknowledge that there are rare inherited variants and de novo variants, which are highly penetrant. These rare inherited variants and de novo variants are estimated to account for approximately 50% of the genetic etiology of ASD and common inherited genetic variants account for approximately one third of ADHD's heritability (Yang 2013, Faraone 2019, Demontis 2023). Further, the heritability calculations do not account for de novo mutations. For these reasons, the referenced statements about the genetic contribution to ASD and ADHD etiology are incomplete and can be misleading." (Chung Report at 66).

In her report, Dr. Chung references Demontis et al. (2023) as support for the rates of rare inherited variants, de novo variants, and common variants in ASD and ADHD. In reviewing this article, I found that common-variant ADHD risk was associated with impaired complex cognition, such as verbal reasoning and a range of executive functions, including attention. It is important to note that genes do not code for diagnoses—they code for symptom domains within and across diagnoses. There is not any gene, no matter how penetrant or rare that is going to code for all of the diagnostic criteria of one disorder. Rather, genes are found for specific symptom domains that will appear transdiagnostically in our current DSM and ICD nosology. Additionally, as referenced in Faraone et al. (2019), the effects of DNA risk variants on ADHD must, individually, be very small. In rare cases, a single genetic defect may lead to ADHD in the absence of other

DNA variants. But, as twin studies show, even highly penetrant gene variants do not always result in the disease, which means that even for such rare variants, the disease is responsive to a gene-environment interaction. It is equally clear that no common DNA variants are necessary and sufficient causes of ADHD. The heritability that cannot be explained by main effects of rare or common variants is likely due to gene−environment interactions or gene−environment correlations. And the weak contribution of all common variants in ADHD, and even rare variants, may require an environmental second hit.

A genome wide association study has demonstrated that the etiology of ADHD is much better explained by the interaction of genes with environment rather than by genes alone (Czamara et al., 2019, Figure 7b).

I. Claim that There Is Inadequate Support for CYP2E1 in the Brain

In his report, Dr. McGill claims that Plaintiffs' experts provide insufficient evidence to support their assertion that the CYP2E1 enzyme is present in the adult brain or fetal brain. (McGill Report at 58). Specifically, Dr. McGill criticizes Ghanem, et al. (2016) for summarizing data from other studies to support the claim that "CYP2E1, one of the CYPs isoforms involved in APAP bioactivation by the liver, is also expressed in the brain." (McGill Report at 58). McGill further criticizes that "Joshi and Tyndale (2006) examined brain samples from adult male rats, Upadhya et al. (2000) examined brain samples from adult humans, and Howard et al. (2003) examined brain samples from adult rats and adult humans. None of the three studies examined embryonic or fetal brain. These studies also did not address glutathione levels in brain or whether they are sufficient to detoxify NAPQI in the embryonic/fetal brain. These studies are insufficient to support the position that maternal use of acetaminophen damages embryonic/fetal brain leading to ASD and/or ADHD through a mechanism involving excess NAPQI production." (McGill Report at 58).

Dr. McGill fails to acknowledge that, as cited in Dr. Cabrera's amended report, the brain produces CYP2E1 as well as other P450 cytochromes in multiple regions: the frontal lobe, cerebellum, occipital lobe, and pons regions. (Cabrera Amended Report at 60). This means that APAP present in the brain can metabolize into NAPQI. As shown by the studies cited in Dr. Cabrera's report, CYP2E1 is found in animal brains (mouse, rat, and monkey) as well as prenatal human brain. Additionally, epigenetic changes were shown in CYP2E1 in placentas from the MARBLES ASD study. Thus, all brain regions examined and prenatal human brains can produce NAPQI.

VI. CONCLUSION

In conclusion, after weighing the scientific evidence reviewed in preparation of my Initial Report and this report, applying the Bradford-Hill elements, and using my clinical and research experience, training, and education, I opine to a reasonable degree of medical and scientific certainty that prenatal exposure to APAP can cause the neurodevelopmental disorders of ASD and ADHD.

I hold the foregoing opinions to a reasonable degree of medical and scientific certainty.

Dated: June 28, 2023

Respectfully submitted,

Eric Hollander MD

Eric Hollander, M.D.